These natural antitoxins were first described by Boas[6] as "protective factors X" and afterward named "vitamin H" by György.[7] It has been recently shown, however, that "vitamin H" is identical with biotin.

Applying the newer microbiological techniques, it is currently shown by the Cleveland-Texas cooperative group that fresh egg albumin is capable of inactivating biotin *in vitro,* due to the formation of a stable and relatively undigestible biotin-albumin conjugate. György and his colleagues have tentatively suggested the term "avidalbumin" (literally, "hungry" or "vitaminophagic" albumin) for this biotin-binding protein. They believe that its biotin-binding capacity is an adequate explanation for the apparent "toxic" effects of raw egg. This was adequately verified by animal experimentation. Microbiological assays of the tissues of egg-white injured animals, for example, invariably showed a marked deficiency in tissue biotin, in spite of the fact that more than adequate amounts of biotin were present in the gastro-intestinal tract. Intestinal absorption of nutritional biotin was apparently completely blocked. Or, if minor absorption did take place, it was in the form of a biologically inert biotin-albumin conjugate. The "toxic" effects of egg white are thus merely secondary effects due to fractional (biotin) tissue starvation.

György and his colleagues have thus suggested a new principle in nutritional pathology which, in time, may be shown to have numerous other clinical applications. Popular apprehension, however, should be prevented at this time by emphasizing the fact that egg white loses its "toxicity" on adequate cooking,[8] and that cabbage, spinach and many other vegetables, as well as liver, kidney, and cow's milk, have high prophylactic and curative values. Summer milk is superior to winter milk in this regard, though both are effective with experimental animals. Meanwhile, biological theorists may be puzzled to assign a teleological rôle to this biotin-binding protein.

P. O. Box 51.

W. H. Manwaring,
Stanford University.

6 Boas, M. A.: Biochem. Jour., 21:712, 1927.

7 György, P.: Z. ärztl. Fortbild., 28:377, 417, 1931.

8 Parsons, H. T., and Kelly, E.: Amer. Jour. Physiol., 104:150, 1933.

In California one of the first local health regulations was passed in San Francisco which prohibited the shooting of buzzards and other birds that might consume carrion. In Sacramento, in 1850, an ordinance was passed which required the daily removal of garbage, waste, and refuse. The epidemic of cholera that invaded Sacramento in 1850, and again in 1852, was the factor that caused the early passage of this legislation.

The most common nuisances reported to health officers are odor nuisances. To be sure, very few, if any odor nuisances, are detrimental to individual health, although they may constitute offenses to the senses, and may be very disturbing to the comfort of the individuals concerned.

ORIGINAL ARTICLES

LEUKEMIA: EVALUATION OF THE THERAPY*

S. P. Lucia, M. D.
San Francisco

INTRODUCTION and Definition.—The term "leukemia" signifies a pathologic condition characterized by dysplasia of the hematopoietic tissues, often with evidences of widespread metastases and tumors in distant organs, and usually with the striking feature of a leukocytosis of immature cells in the peripheral blood. In so far as the bone marrow is concerned, it is usually hyperplastic and, in some instances, the leukemic process may manifest itself as a true tumor of the hematopoietic tissues. The immature circulating leukocytes in the blood stream are to be considered permanent metastases. Leukemia simulates cancer in the following ways: the leukemic cell loses its ability to mature (growth proceeds uncontrolled); there is a tendency to form secondary metastatic foci; the metabolic rate of the immature cells is similar to that of neoplasms; the cells maturate under the influence of roentgen irradiation; the disease is not transmissible by inoculation; and, finally, like cancer, the clinical course is marked by cachexia and a fatal termination. The leukemic reaction in the bone marrow and lymph glands is in all probability initiated by chemical changes in the body fluids, which bathe these vulnerable tissues and their definitive cells.

The incidence of leukemia is increasing out of all proportion to the facility of its diagnosis. During this past spring, unusual and bizarre clinical types of leukemia have been quite common. One wonders what part alterations in the diet, the habitual use of powerful medications (often self-prescribed), and the sinister attack of the virus diseases play in these unusual reactions. Clinically, leukemias differ in their degree of malignancy. Some types of leukemia react like fixed tissue tumors and produce distress by mechanical pressure, while other types freely invade the distant tissues. Some are held in abeyance by careful treatment, some remit spontaneously, and some appear to exhibit the characteristics of infections. Often an infection may stimulate the marrow to the point of provoking leukemia.

In order to facilitate the discussion of the treatment of leukemia, it seems advisable to give a simple classification of the clinical forms of the disease. Fatigue, enlarged lymph glands, splenomegaly, hepatomegaly, and an increased tendency to bleed are the cardinal signs of leukemia.

CLINICAL TYPES OF LEUKEMIA

1. In the purely hematologic variety, the diagnosis may be made incidental to a routine blood count, the patient being totally unaware of the dis-

* From the Department of Medicine, University of California Medical School, San Francisco.

Read before the Section on General Medicine at the seventieth annual session of the California Medical Association, Del Monte, May 5-8, 1941.

ease or any of its symptoms. This form is not uncommon. Often the precise diagnosis is not easily determined because of the difficulty in differentiating leukemia from the myeloid reactions secondary to infections.

2. A second variety of leukemia is characterized by an increased basal metabolic rate, with symptoms of fever, tachycardia, hyperidrosis, loss of weight, nervousness, weakness, minor gastro-intestinal symptoms, and cachexia.

3. A third variety is characterized by enlargement of abdominal viscera (liver and spleen) with or without lymphadenopathy. Here the symptoms are referable to the enlarged organs and to the mechanical difficulties they produce, such as pressure, pain, cough, urinary frequency, diarrhea or constipation, occasionally arthritis, and not infrequently neuritis.

4. A fourth variety is characterized by anemia, weakness, and signs of myocardial insufficiency. Here the symptoms are due to the effects of the decreased oxygen-carrying capacity of the blood. The cardinal symptoms are pallor, weakness, dizziness, fatigue, and edema.

5. A fifth variety is characterized by an abnormal tendency to bleed and occasionally by thrombosis. Usually the signs and symptoms of this variety connote an advanced stage of one of the other forms of the disease.

The variations in the intensity and clinical character of the leukemic disease process, in a given individual, suggest that perhaps the nature of the stimulating agent, as well as the biologic characteristics of the host, conditions the type of the disease.

Since there is no known method of cure, all treatments of leukemia should be regarded as empirical and have as its objective the symptomatic relief of the patient. Furthermore, it is not justifiable to institute practices which may throw out of equilibrium the general tissue defense mechanisms of the body. A greater measure of success will come to him who pays particular attention to the minor details of treatment.

GENERAL MEASURES OF TREATMENT

Since the patient afflicted with leukemia suffers from weakness and lack of energy, due primarily to the anemia, rest and limitation of activity should be prescriptive. He should be taught to live within his physical capital. The presence of a high basal metabolic rate, of fever, or of enlargement of the liver and spleen, conditions not only the activity of the patient, but also determines the character of the treatment. Naturally, the diet should be well balanced, high in calories, and high in carbohydrate. In lymphatic leukemia, a diet of low fat content should be prescribed in order to avoid stimulation of the lacteal and lymphatic systems. When diffuse bleeding from mucous surfaces occurs, it is advisable to give a diet ample in vitamin C and high in fat and protein in order to obtain the maximum beneficial effects on the capillaries and on the blood coagulation mechanism. In so far as climate is concerned, undue exposure to sunlight should be discouraged. Patients suffering from leukemia should be advised to avoid sunburn. The oral hygiene of the leukemic patient should be scrupulous, since oral sepsis is common in this disease. The use of a soft toothbrush, sodium perborate, hydrogen peroxide, and, occasionally, warm sodium bicarbonate solutions are advised. For breaks in the mucous membrane, a one per cent aqueous solution of gentian violet may be used, and there are advantages to be gained in the routine use of astringent mouth washes.

Since the treatment of the patient with leukemia is primarily symptomatic, it would seem advisable to list the criteria upon which the selection of cases for treatment is based. Consider treatment:

1. When the leukocyte count is over 200,000, and institute it when the count is over 400,000. Do not treat the leukocytosis alone.

2. When the effects of mechanical pressure produce symptoms.

3. When there is a marked and progressive anemia.

4. When weight loss is a prominent factor, and especially when it is due to gastro-intestinal dysfunction.

5. When there are hemorrhagic manifestations.
6. When the temperature remains elevated.
7. When the basal metabolic rate is high.

THERAPEUTIC AGENTS IN THE TREATMENT OF LEUKEMIA

1. *Biologic Agents.*—Capps and Smith (1907) demonstrated the presence of leukocytolytic substances in the serum of treated leukemic patients. These substances were capable of destroying leukocytes *in vitro* and of producing leukopenia when injected into animals. When given to patients, they produced only transitory diminutions in the leukocyte count. Immune substances are ineffective in the treatment of human leukemia, although they may be of value in the treatment of the virus leukemia of fowl. The use of Coley's toxin (streptococcus and prodigiosus) is warrantable in the treatment of Hodgkin's disease, although its effectiveness may be attributed to the foreign protein reaction which it produces. Inoculation of the leukemic patient with malaria plasmodia is not defensible on the evidence so far presented, despite the fact that it produces fever, leukopenia, and retardation of the activity of the bone marrow. Extracts of liver, spleen, bone marrow, lymph glands, and fetal tissues are too variable to be classed as effective therapeutic agents, although there is some evidence to show that, perhaps, liver extract may have a limited use in the treatment of leukemia. Transfusions are useful in the treatment of leukemia when hemorrhage threatens life and when marked anemia is present. When anemia is accompanied by leukopenia, and under circumstances when the use of irradiation is prohibitive, transfusion remains the only rational therapeutic measure.

2. *Chemical Agents.*—Arsenic, introduced by Lissauer in 1865, and its allies, antimony, bismuth and phosphorus, are perhaps the most effective chemotherapeutic agents for the treatment of leukemia. Arsenic is especially valuable in the

treatment of early cases of myeloid leukemia. Frequently it helps postpone treatment by irradiation, thereby prolonging the period of survival. Although arsenic is of some value in the treatment of chronic lymphatic leukemia, it is most effective in the treatment of chronic myeloid leukemia. One should give arsenic in rapidly increasing doses until toxic symptoms occur, and thereafter continue the maximum tolerated dose until the leukocyte count drops to normal levels. Subsequently the dosage may be diminished to the minimum, and it is my belief that the leukemic patient should never discontinue its use. In the treatment of chronic myeloid leukemia with arsenic, one may expect symptomatic improvement, remission of the leukemia, a decrease in the leukocyte count, a reduction in the number of immature leukocytes and nucleated red blood cells in the blood stream, and a decrease in the size of the spleen, liver, and lymph glands.

The average dose of arsenic, as Fowler's solution, is three minims, three times a day, increasing by one minim per dose per day to a maximum of 12 to 15 minims three times a day, then reducing the dose by one minim per dose per day and continuing in cycles until the desired effect is obtained. The maintenance dose of Fowler's solution may be established at levels as low as 2 to 3 minims, two to three times a day. Some hematologists give the maximum tolerated dose until the leukocyte count is reduced to normal levels before reducing the dosage.

The toxic symptoms of arsenic therapy are chemosis, coryza, pseudo-erysipelas, urticaria, gastro-intestinal symptoms (irritation, nausea, vomiting, and diarrhea) herpes, neuritis, hyperpigmentation, and hyperkeratosis. Therefore, patients taking arsenic should be carefully observed for signs of toxicity. Occasionally arsenic therapy, combined with irradiation therapy, is found to be the best treatment in chronic myeloid leukemia.

As noted above, antimony, bismuth and phosphorus belong to the same chemical group as arsenic. All of these agents induce leukopenia and depress the erythropoietic tissues. Antimony, however, exhibits the least toxic effect on the erythropoietic function of the marrow. It is less effective than arsenic in reducing the size of the spleen, liver, and lymph glands. Soon radio-active compounds of antimony, arsenic, and bismuth may be available, so that the effects of these agents may be compared with those of radio-active phosphorus which will be described below.

Another potent agent in the treatment of leukemia is benzol, introduced by Koranyi in 1912. A 50 per cent solution in olive oil is given orally in capsules in doses of 3 to 5 grams a day. Benzol is a powerful but highly toxic drug, capable of producing aplasia of the marrow. The use of benzol should be discontinued when the white blood cell count drops to 20,000. Benzol may be used as an adjuvant to irradiation therapy, and it may prove effective in the x-ray fast case.

Friedgood (1932) reintroduced the use of Lugol's solution to alleviate the symptoms secondary to an elevated basal metabolic rate in chronic lymphatic leukemia. My own experience corroborates the observations of Friedgood.

The alkaloidal active principle of meadow saffron (Colchicum autumnale), colchicine, has been effectively used by some workers to arrest the growth of developing tumor cells at the metaphase. It is easy to destroy tissue, but to destroy differentially is a difficult problem, and it appears that in colchicine we have an agent to assist us in this problem. At certain critical concentrations of colchicine in living tissues, Dixon found that the mitosis of developing cells was accelerated up to the stage of the metaphase, at which point it was subsequently arrested and the cells failed to develop further. From this information it would appear that colchicine would be most effective in the treatment of those leukemias characterized by markedly increased numbers of primitive blast cells. The recommended dosage of colchicine is one-half milligram, three times a day, and increasing the dose by one-half milligram daily up to the point of toxicity. The effective tissue concentration of colchicine is given as 1 to 8,000,000. Colchicine is highly toxic, and symptoms such as salivation, nausea, vomiting, gastric pain, diarrhea, and weakness have been recorded with doses of 4 to 5 milligrams. I have not observed any dramatic effects in the treatment of chronic leukemia, perhaps owing to the fact that the cells are already too highly differentiated. It appears to be indicated in the treatment of acute leukemia, because of the increased rate of development and the degree of immaturity of the blast cells in this disease. It would be logical to use colchicine in those leukemias in which the proportion of blast cells is high and in which irradiation therapy is desirable.

There are some reports concerning the use of quinin in the treatment of leukemia. This medicament depresses leukocytopoiesis; however, it is less effective than arsenic.

Colloidal gold, silver, sulphur, and lead have also been used. These agents produce an effective leukopenia, but they are dangerous in that they may induce malignant leukopenia, bone marrow aplasia, or fatal purpura.

Other chemical agents, such as ergot, sodium sulfocyanate, cinnamic acid, naphthalene-tetrachlorid, amidopyrin, neocinchophen, and members of the para-aminobenzenesulfonamid group have been used. In some individuals these will produce transient diminutions in the leukocyte count. The use of iron for the treatment of leukemia is not defensible, although it may be effective in the treatment of the anemia of some leukemias.

3. *Physical Agents.*—Since the life expectancy of the patient with leukemia is roughly three and a half years, it behooves us to advance carefully, keeping in mind that at best our therapy is a compromise. We must remember that even normal man may be rendered more susceptible to the spontaneous occurrence of leukemia after exposure to roentgen-rays. Contrary to the opinion of many, chronic leukemia may often be converted into acute leukemia by irradiation or infection. Infections, by and large, prove devastating to the leukemic

patient; this may be due in part to the fact that the leukemic organism does not produce immune bodies effectively. I have never seen a leukemic patient benefited by an intercurrent infection—quite the contrary, it has usually proved disastrous.

Roentgen Irradiation.—To date, the gamma ray has proved to be the most effective and universal therapeutic agent in leukemia. Senn (1903) was the first to treat leukemia with x-ray. Fundamentally, irradiation aims to destroy tissue; ideally we wish it to destroy selectively the offending cell.

Although the mechanism of the effectiveness of irradiation in the treatment of leukemia is not known, there is some evidence to show that the beneficial effects are brought about by hastening the maturation of cells. Isaacs (1926) demonstrated that small to moderate doses of x-rays are stimulative and that, whereas the differentiated cells—myelocytes and lymphocytes—are stimulated to hastened maturity since they have lost their normal power of cell division, the myeloblast and the lymphoblast are stimulated to increased multiplication because they have not yet acquired the ability to maturate normally.

The General Indications for Irradiation Therapy. Each case is a law unto itself, and the best results are obtained by close coöperation between hematologist and roentgenologist. When pressure symptoms, exceedingly high leukocyte counts, or evidences of progressive invasion of the bone marrow occur, it is necessary that roentgen-ray therapy be instituted. Naturally, one must be guided by the character of the disease, the size of the splenic tumor, the blood counts, the general condition of the skin and capillaries, and the general appearance and well-being of the patient. It must be remembered that the patient may live in harmonious equilibrium with his disease, and that the physician should aim to assist in its active combat, thereby bending every effort toward enhancing the active defense mechanisms. The control of leukemia is exceedingly difficult when the tissue reactions of the host are purely passive. Furthermore, leukemia becomes more and more resistant with each course of irradiation. The reward for too vigorous treatment is a short remission and a more rapid recurrence. It is advisable to use small, fractional doses of irradiation, and the least total dose which will produce an effective remission. By the use of small doses, too rapid regression of leukemic deposits, and marked and unintended reactions are avoided. It should be remembered that some hosts do not take irradiation well, and, conversely, that some leukemias are particularly sensitive. It is well to remember that the total effective dose of irradiation in any given case is fixed, and, therefore, it should be used sparingly, carefully, and wisely.

The site of treatment in leukemia will depend upon the type. In myeloid leukemia, it is logical to treat the bone marrow or an enlarged organ, known to contain the offending cells in active growth. The effects of local treatment are reflected throughout the body. Irradiation of the spleen alone in myeloid leukemia is usually adequate, and aside from the specific effects there is an unexplained "excellent general effect." This is attributed to the fact that the large volume of blood circulating through the lungs and heart is also irradiated.

In lymphatic leukemia it is logical to irradiate the enlarged lymph nodes, then the spleen and eventually the bone marrow. The lymphatic infiltrations of the bone marrow do not, as a rule, regress following irradiation to other parts of the body; therefore the roentgen rays must be directed to the bone marrow when it is known or suspected that lymphatic infiltrations exist there.

When anemia is a disturbing factor during the course of treatment of leukemia, it is advisable to irradiate the long and flat bones. Duke (1923) advocates irradiation of the chest in order to affect the greatest volume of blood, concluding that the important systemic effects are mediated through the surcharged irradiated blood. Dale (1931) advises treating the entire body. This method has proved quite useful in the treatment of certain refractive cases of lymphatic leukemia.

In roentgen irradiation do not aim to reduce the leukocyte count to normal. An increase in the hemoglobin and red blood cell content indicates that irradiation is effective. Conversely, a marked drop in hemoglobin and red blood cell content indicates an unfavorable reaction or overirradiation. In lymphatic leukemia it may be necessary to treat the bone marrow if the hemoglobin and red blood cell content remain unaltered after the leukocyte count has dropped and the lymphadenopathy and splenomegaly have regressed, although the general clinical condition of the patient is perhaps the most important single guiding factor in the treatment.

Discontinue irradiation therapy when there is:

1. A too rapid decrease in the leukocyte count.
2. Reduction in the hemoglobin and red blood cell content during treatment.
3. Increasing numbers of primitive blast cells in the peripheral blood.
4. Evidence of decreasing vitality.

Other forms of gamma irradiation therapy, such as radium, are not justifiable unless roentgen therapy is not available, or the patients cannot be moved to hospitals.

Radio-active Phosphorus.—The use of beta rays (radio-active phosphorus) in the treatment of leukemia is still in its infancy. It is possible that soon great advances may be forthcoming. Radio-active phosphorus, like ordinary phosphorus, localizes in the bone marrow; therefore we have a means of bringing potent beta rays to the point of active formation of the pathological cells, especially in myeloid leukemia. In general, radio-active phosphorus is distributed and deposited throughout the marrow. It has a tendency also to seek leukemic infiltrations elsewhere in the body. Another interesting fact is that the leukemic patient exhibits a more rapid uptake of radio-active phosphorus than the normal person. The biologic phenomena of phosphorus and the peculiarity of the physical characteristics of radio-active phosphorus make available for us a potent weapon in the treatment of leukemia. The future should bring us definite and much-desired information on this therapeutic agent.

AXIOMS IN THE DIAGNOSIS AND TREATMENT OF LEUKEMIA

It is possible from the above discussion to formulate a few of the aforementioned principles as axioms:

1. The blood should be counted before, and at frequent intervals, during the active treatment of leukemia.

2. Do not treat a leukocytosis.

3. Cutaneous lesions are of diagnostic importance, since they are more common in Hodgkin's disease and lymphatic leukemia than in myelogenous leukemia.

4. Purpuric hemorrhages and petechiae suggest advanced stages of leukemia, in contrast to the sudden hemorrhages from the mucous membranes and oral cavity in acute leukemia.

5. The appearance of infiltration of the retinae, or of palpable lymph nodes, in the course of myeloid leukemia is decidedly unfavorable. It connotes a terminal stage of the disease.

6. The anemia in leukemia is due to the leukemia. It is usually alleviated in the course of treatment; if not, the prognosis is grave.

7. A high blast count is an unfavorable sign, especially when it occurs in the course of x-ray therapy.

8. An early death in the course of lymphatic leukemia is usually due to infection, because the myeloid cells (phagocytes) are depressed or absent.

9. Do not biopsy tissues unless it is absolutely necessary, because the leukemic processes at the site of the incision may become aggravated.

10. It is advisable to reserve irradiation for the treatment of mechanical disturbances arising in the course of leukemia.

11. Irradiation appears to hasten the fatal course of acute leukemia.

12. It is more valorous to be conservative in the treatment of acute leukemia. It is rarely benefited by any sort of treatment.

13. Our most hopeful therapeutic agents are, at best, only palliative measures.

14. As a rule it is advisable to irradiate the spleen and liver in myeloid leukemia, and the lymph nodes in lymphatic leukemia.

15. The bone marrow may be advantageously irradiated for the persistent anemia in the course of chronic lymphatic leukemia.

16. The lymph nodes appear to withstand more irradiation, without general constitutional reactions, than the spleen.

17. Massive doses of roentgen irradiation produce edema and swelling before decreasing the size of a leukemic tumor. This phenomenon may prove disastrous in the treatment of tumors around the delicate mediastinal structures.

CONCLUSIONS

1. There is no known method of cure of leukemia.

2. It is advisable to outline a conservative plan in the treatment of leukemia, and to attempt to understand the biologic reactions of the individual unit acting as a whole in his environment.

3. The goal of successful therapy in leukemia is the temporary restoration of the patient to a degree of efficiency, enabling him to live a useful though limited life.

4. At present, irradiation is the best single therapeutic agent in the treatment of leukemia.

5. Arsenic and radio-active elements offer a ray of hope in the chemotherapeusis of leukemia.

University of California Medical School.

SULFONAMIDE GROUP OF DRUGS: GENERAL PROPERTIES, USE AND DOSAGE*

ARTHUR HAIM, M. D.
San Francisco

INTRODUCTION.—Almost five years have passed since the introduction of the sulfonamides into this country. They have been used on an unprecedented scale, and a tremendous wealth of material and reports has accumulated. Many drugs have been developed; only a few, however, have gained sufficient recognition to be included in our review. We shall concern ourselves with sulfanilamide, sulfapyridine, and sulfathiazole. Even this limitation will not make it possible to cover the field adequately. The following speakers will take up the applications in their respective fields, and Doctor Cutting, I hope, will stress in his discussion the pharmacologic principles. Therefore, I take the liberty to restrict my remarks to certain general principles which seem important at this time, and which constitute a present trend as it appears to us. The price for the required brevity of this presentation is a somewhat dogmatic character of my remarks, for which I want to apologize.

HISTORY

It is well known now that sulfanilamide was synthesized and described in 1908. Its chemotherapeutic properties, however, were not adequately appreciated until sufficient interest was awakened by the reports about prontosil as developed by the German workers around 1932-1934. In 1935, French investigators were able to demonstrate, in extensive animal experiments, that the chemotherapeutic results of prontosil could also be obtained with a simpler radical, contained in the complex prontosil molecule. This radical, sulfanilamide, reached the United States in 1936 at the same time as did prontosil. The latter was mainly used in conditions where sulfanilamide could not be given by mouth, while prontosil was available in a sterile stable solution.

In 1938, sulfapyridine was developed in England and gained rapid recognition as a potent agent against pneumococci and, to a lesser degree, against staphylococci. It proved, however, to be a much more toxic drug than sulfanilamide. It is for this reason that sulfathiazole, which was developed in this country in 1939, attained widespread popu-

---

* Read before the Section on Eye, Ear, Nose and Throat at the seventieth annual session of the California Medical Association, Del Monte, May 5-8, 1941.